



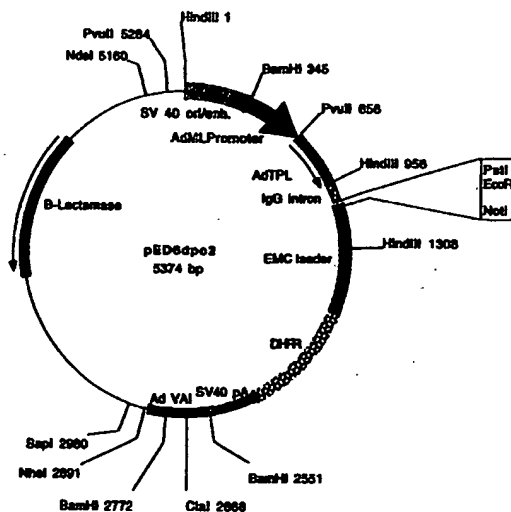
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(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED0dpc2
Plasmid size: 5374 bp

Comments/References: pED0dpc2 is derived from pED0dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al. (1991), NAR 19: 4485-4490.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of Ser. No. 06/XXX,XXX (converted to a provisional application from non-provisional application Ser. No. 08/780,890), filed January 9, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 61 to nucleotide 642;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 89 to nucleotide 440;
- 10 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;
- 15 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;
- 20 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- 25 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 61 to nucleotide 642; the nucleotide sequence of SEQ ID NO:1 from nucleotide 89 to nucleotide 440; the nucleotide sequence of the full-length protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone BI164_1 deposited

under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein
5 comprising the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising
10 a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- (b) the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127;
- 15 (c) fragments of the amino acid sequence of SEQ ID NO:2; and
- (d) the amino acid sequence encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence
20 of SEQ ID NO:2 from amino acid 23 to amino acid 127.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- 25 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1625 to nucleotide 1750;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1484 to nucleotide 1729;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BK445_1 deposited under accession
30 number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;

5 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

10 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

15 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 1625 to nucleotide 1750; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1484 to nucleotide 1729; the nucleotide sequence of the full-length protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290; or the
20 nucleotide sequence of the mature protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein
25 comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group
30 consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

- (d) the amino acid sequence encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 99 to nucleotide 1058;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 644;
- 15 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;
- 20 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- 25 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- 30 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 99 to nucleotide 1058; the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 644; the nucleotide sequence of the full-length protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290; or the
5 nucleotide sequence of the mature protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein
10 comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group
15 consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182;
- (c) fragments of the amino acid sequence of SEQ ID NO:6; and
- 20 (d) the amino acid sequence encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182.

25 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID
30 NO:7 from nucleotide 237 to nucleotide 1184;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 207 to nucleotide 935;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

5 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

10 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

15 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

20 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 237 to nucleotide 1184; the nucleotide sequence of SEQ ID NO:7 from nucleotide 207 to nucleotide 935; the nucleotide sequence of the full-length protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290; or the
25 nucleotide sequence of the mature protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein
30 comprising the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;
- 5 (b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233;
- (c) fragments of the amino acid sequence of SEQ ID NO:8; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;
- 10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 15 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 142 to nucleotide 828;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 522;
- 20 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;
- 25 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;
- 30 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

5 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 142 to nucleotide 828; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 522; the nucleotide sequence of the full-length protein
10 coding sequence of clone CW924_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290. In yet other preferred
15 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

20 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to
25 amino acid 127;
- (c) fragments of the amino acid sequence of SEQ ID NO:10; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such
30 protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 3 to nucleotide 1937;
- 5 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 204 to nucleotide 414;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;
- 10 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;
- 15 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;
- 20 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- 25 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 3 to nucleotide 1937; the nucleotide sequence of SEQ ID NO:11 from nucleotide 204 to nucleotide 414; the nucleotide sequence of the full-length protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290. In yet other preferred

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embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ
5 ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- 10 (b) the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137;
- (c) fragments of the amino acid sequence of SEQ ID NO:12; and
- (d) the amino acid sequence encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;
- 15 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 20 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 137 to nucleotide 457;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
25 NO:13 from nucleotide 323 to nucleotide 457;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 82 to nucleotide 322;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DM406_1 deposited under accession
30 number ATCC 98290;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 137 to nucleotide 457; the nucleotide sequence of SEQ ID NO:13 from nucleotide 323 to nucleotide 457; the nucleotide sequence of SEQ ID NO:13 from nucleotide 82 to nucleotide 322; the nucleotide sequence of the full-length protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62;

(c) fragments of the amino acid sequence of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone

5 DM406_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14 or the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62.

10 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 312 to nucleotide 851;

15 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 56 to nucleotide 470;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

20 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

25 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

30 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 312 to nucleotide 851; the nucleotide sequence of SEQ ID NO:15 from nucleotide 56 to nucleotide 470; the nucleotide sequence of the full-length protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
 - (b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53;
 - (c) fragments of the amino acid sequence of SEQ ID NO:16; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 541;

- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 272 to nucleotide 541;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 448;
- 5 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;
- 10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;
- 15 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- 20 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions, to any one of the polynucleotides specified in (a)-(j).
- 25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 541; the nucleotide sequence of SEQ ID NO:17 from nucleotide 272 to nucleotide 541; the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 448; the nucleotide sequence of the full-length protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290; or the
- 30 nucleotide sequence of the mature protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein

comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

5. In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:18;
- (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to
10 amino acid 143;
- (c) fragments of the amino acid sequence of SEQ ID NO:18; and
- (d) the amino acid sequence encoded by the cDNA insert of clone
EH203_2 deposited under accession number ATCC 98290;

- the protein being substantially free from other mammalian proteins. Preferably such
15 protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143.

- In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.
20 Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such
25 polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

- 30 Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically

effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

- 5 Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

- 10 Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid
15 sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

- 20 As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins
25 which are transported across the membrane of the endoplasmic reticulum.

Clone "BI164_1"

- A polynucleotide of the present invention has been identified as clone "BI164_1". BI164_1 was isolated from a human fetal kidney cDNA library using methods which are
30 selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BI164_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BI164_1 protein").

The nucleotide sequence of BI164_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BI164_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

- 5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BI164_1 should be approximately 800 bp.

The nucleotide sequence disclosed herein for BI164_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BI164_1 demonstrated at least some similarity with sequences
10 identified as AA169106 (ms65e05.r1 Stratagene mouse embryonic carcinoma (#937317) Mus musculus cDNA clone 616448 5'), AA568401 (nf16b11.s1 NCI_CGAP_Pr1 Homo sapiens cDNA clone IMAGE:913917 similar to contains element TAR1 repetitive element), and AA579465 (nf29h01.s1 NCI_CGAP_Pr1 Homo sapiens cDNA clone IMAGE:915217). Based upon sequence similarity, BI164_1 proteins and each similar protein or peptide may
15 share at least some activity.

Clone "BK445_1"

A polynucleotide of the present invention has been identified as clone "BK445_1". BK445_1 was isolated from a human adult retina cDNA library using methods which are
20 selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BK445_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BK445_1 protein").

- 25 The nucleotide sequence of BK445_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BK445_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone
30 BK445_1 should be approximately 3400 bp.

The nucleotide sequence disclosed herein for BK445_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BK445_1 demonstrated at least some similarity with sequences identified as F08866 (H. sapiens partial cDNA sequence; clone c-2th07), M87889 (Human

carcinoma cell-derived Alu RNA transcript, clone CD140), U52111 (Human Xq28 genomic DNA in the region of the ALD locus containing the genes for creatine transporter (SLC6A8), CDM, adrenoleukodystrophy (ALD), Na⁺-isocitrate dehydrogenase gamma), and Z69649 (Human DNA sequence from cosmid L69F7B, Huntington's Disease Region, chromosome 4p16.3 contains Huntington Disease (HD) gene). The predicted amino acid sequence disclosed herein for BK445_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BK445_1 protein demonstrated at least some similarity to sequences identified as L24521 (transformation-related protein [Homo sapiens]) and U22376 (alternatively spliced product using exon 13A [Homo sapiens]). Based upon sequence similarity, BK445_1 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of BK445_1 indicates that it may contain an Alu repetitive element.

Clone "BP101_2"

A polynucleotide of the present invention has been identified as clone "BP101_2". BP101_2 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BP101_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BP101_2 protein").

The nucleotide sequence of BP101_2 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BP101_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Another possible reading frame and predicted amino acid sequence encoded by BP101_2 is encoded by nucleotides 992-1912 of SEQ ID NO:5 and is reported in SEQ ID NO:28; this alternative open reading frame could be joined to the reading frame reported in SEQ ID NO:6 if an insertion or deletion resulting in a frameshift was made in the sequence of SEQ ID NO:5. Amino acids 126 to 138 of SEQ ID NO:28 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 139 of SEQ ID NO:28, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BP101_2 should be approximately 2280 bp.

The nucleotide sequence disclosed herein for BP101_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BP101_2 demonstrated at least some similarity with sequences identified as M87918 (Human carcinoma cell-derived Alu RNA transcript, clone NE51),
5 N74481 (za54d08.s1 Homo sapiens cDNA clone 296367 3' similar to contains Alu repetitive element), and W03189 (za54d08.r1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone 296367 5'). The predicted amino acid sequence disclosed herein for BP101_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BP101_2 protein demonstrated at least some
10 similarity to sequences identified as L11672 (zinc finger protein [Homo sapiens]). Based upon sequence similarity, BP101_2 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of BP101_2 indicates that it may contain an Alu repetitive element.

15 Clone "CD124_3"

A polynucleotide of the present invention has been identified as clone "CD124_3". CD124_3 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer
20 analysis of the amino acid sequence of the encoded protein. CD124_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CD124_3 protein").

The nucleotide sequence of CD124_3 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the
25 predicted amino acid sequence of the CD124_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CD124_3 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for CD124_3 was searched against the
30 GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CD124_3 demonstrated at least some similarity with sequences identified as AA123334 (mq10f01.r1 Barstead MPLRB1 Mus musculus cDNA clone 578329 5'), AA215297 (zr94b03.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone), AA361664 (EST71136 T-cell lymphoma Homo sapiens cDNA 5' end), M16362 (Mouse opa repeat

mRNA, 3' end (MOUSE)), N56580 (SH2201F Homo sapiens cDNA clone), Q12515 (CSP-2 peptide from *P. falciparum* (clone 4)), W53105 (md14d02.r1 Soares mouse embryo NbME13.5 14.5 *Mus musculus* cDNA clone 368355 5'), and X78609 (*G.gallus* genomic DNA repeat region, clone 16E1). Based upon sequence similarity, CD124_3 proteins and
5 each similar protein or peptide may share at least some activity. The nucleotide sequence of CD124_3 indicates that it may contain a simple repeat sequence and a chicken genomic repeat sequence.

Clone "CW924_1"

10 A polynucleotide of the present invention has been identified as clone "CW924_1". CW924_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CW924_1 is a full-length
15 clone, including the entire coding sequence of a secreted protein (also referred to herein as "CW924_1 protein").

The nucleotide sequence of CW924_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CW924_1 protein corresponding to the foregoing
20 nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CW924_1 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for CW924_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and
25 FASTA search protocols. CW924_1 demonstrated at least some similarity with sequences identified as H86434 (ys93h08.r1 Homo sapiens cDNA clone 222399 5'), T15605 (IB1619 Infant brain, Bento Soares Homo sapiens cDNA 3'end similar to IB570 H. sapiens brain cDNA clone IB570), U17259 (*Mus musculus* p19 mRNA, complete cds (MOUSE)), and W54334 (md05b08.r1 Soares mouse embryo NbME13.5 14.5 *Mus musculus* cDNA clone
30 367479 5'). The predicted amino acid sequence disclosed herein for CW924_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CW924_1 protein demonstrated at least some similarity to sequences identified as P50649 (Sequence encoded by brain specific (Class III) clone p1A75 ORF 1) and U17259 (p19 [*Mus musculus*]). The predicted CW924_1 protein

also demonstrated at least some similarity to mouse p21 protein. Based upon sequence similarity, CW924_1 proteins and each similar protein or peptide may share at least some activity. Amino acids 74 to 86 of SEQ ID NO:10 are a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 87, or are a transmembrane domain.

Clone "DF518_3"

A polynucleotide of the present invention has been identified as clone "DF518_3". DF518_3 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DF518_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "DF518_3 protein").

The nucleotide sequence of DF518_3 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DF518_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DF518_3 should be approximately 2650 bp.

The nucleotide sequence disclosed herein for DF518_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DF518_3 demonstrated at least some similarity with sequences identified as AA190696 (zp89a02.r1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 627338 5'), H13983 (EST00009 Homo sapiens genomic clone C1-14 5'), and T90095 (yd39d08.s1 Homo sapiens cDNA clone 110607 3'). Based upon sequence similarity, DF518_3 proteins and each similar protein or peptide may share at least some activity.

Clone "DM406_1"

A polynucleotide of the present invention has been identified as clone "DM406_1". DM406_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DM406_1 is a full-length

clone, including the entire coding sequence of a secreted protein (also referred to herein as "DM406_1 protein").

The nucleotide sequence of DM406_1 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DM406_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Amino acids 50 to 62 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 63, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DM406_1 should be approximately 1700 bp.

The nucleotide sequence disclosed herein for DM406_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DM406_1 demonstrated at least some similarity with sequences identified as D82016 (Human fetal brain cDNA 5'-end GEN-430G10) and H12174 (ym17f08.r1 Homo sapiens cDNA clone 48073 5'). Based upon sequence similarity, DM406_1 proteins and each similar protein or peptide may share at least some activity.

Clone "EH189_1"

A polynucleotide of the present invention has been identified as clone "EH189_1". EH189_1 was isolated from a human adult blood (peripheral blood mononuclear cells treated *in vivo* with granulocyte-colony stimulating factor) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. EH189_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "EH189_1 protein").

The nucleotide sequence of EH189_1 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the EH189_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone EH189_1 should be approximately 1450 bp.

The nucleotide sequence disclosed herein for EH189_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and

FASTA search protocols. EH189_1 demonstrated at least some similarity with sequences identified as AA681168 (vr75f04.s1 Knowles Solter mouse 2 cell Mus musculus cDNA clone 1134559 5'). Based upon sequence similarity, EH189_1 proteins and each similar protein or peptide may share at least some activity.

5

Clone "EH203_2"

A polynucleotide of the present invention has been identified as clone "EH203_2". EH203_2 was isolated from a human adult blood (peripheral blood mononuclear cells treated *in vivo* with granulocyte-colony stimulating factor) cDNA library using methods
10 which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. EH203_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "EH203_2 protein").

15 The nucleotide sequence of EH203_2 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the EH203_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 1 to 84 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at
20 amino acid 85, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone EH203_2 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for EH203_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and
25 FASTA search protocols. EH203_2 demonstrated at least some similarity with sequences identified as AA482321 (ab15c05.r1 Stratagene lung (#937210) Homo sapiens cDNA clone 840872 5'), H56345 (yq97b12.s1 Homo sapiens cDNA clone 203711 3'), T92363 (ye19h06.s1 Homo sapiens cDNA clone 118235 3'). Based upon sequence similarity, EH203_2 proteins and each similar protein or peptide may share at least some activity.

30

Deposit of Clones

Clones BI164_1, BK445_1, BP101_2, CD124_3, CW924_1, DF518_3, DM406_1, EH189_1, and EH203_2 were deposited on January 8, 1997 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the

accession number ATCC 98290, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

5 Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from
 10 pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse
 15 orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

20 Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the
 25 oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

<u>Clone</u>	<u>Probe Sequence</u>
BI164_1	SEQ ID NO:19
30 BK445_1	SEQ ID NO:20
BP101_2	SEQ ID NO:21
CD124_3	SEQ ID NO:22
CW924_1	SEQ ID NO:23
DF518_3	SEQ ID NO:24

DM406_1

SEQ ID NO:25

EH189_1

SEQ ID NO:26

EH203_2

SEQ ID NO:27

- 5 In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).
- 10 The design of the oligonucleotide probe should preferably follow these parameters:
- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
 - (b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each
- 15 A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with γ - ^{32}P ATP (specific activity 6000 Ci/mmol) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established

20 methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4×10^6 dpm/pmol.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 μl of the stock used to inoculate a sterile culture flask containing 25 ml

25 of sterile L-broth containing ampicillin at 100 $\mu\text{g}/\text{ml}$. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100

30 $\mu\text{g}/\text{ml}$ and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at
5 a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The
10 filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis,
15 hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S.
20 McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion
25 could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence
30 listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated
5 expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed
10 sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s)
15 corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-
20 39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce
25 gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through
30 deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination,

preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably
5 are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor),
10 the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

15 Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing
20 the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most
25 preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or
30 polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides .

- 5 The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

- The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency
- 10 conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [‡]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
5	A	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
	B	<50	T _B [*] ; 1xSSC	T _B [*] ; 1xSSC
	C	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
	D	<50	T _D [*] ; 1xSSC	T _D [*] ; 1xSSC
	E	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
	F	<50	T _F [*] ; 1xSSC	T _F [*] ; 1xSSC
10	G	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
	H	<50	T _H [*] ; 4xSSC	T _H [*] ; 4xSSC
	I	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
	J	<50	T _J [*] ; 4xSSC	T _J [*] ; 4xSSC
	K	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
	L	<50	T _L [*] ; 2xSSC	T _L [*] ; 2xSSC
15	M	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
	N	<50	T _N [*] ; 6xSSC	T _N [*] ; 6xSSC
	O	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
	P	<50	T _P [*] ; 6xSSC	T _P [*] ; 6xSSC
	Q	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
	R	<50	T _R [*] ; 4xSSC	T _R [*] ; 4xSSC

[‡]: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

[†]: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

^{*}T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6(log₁₀[Na⁺]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds.,

- 5 John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or
10 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an
15 expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably
20 linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the
25 protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

30 Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant

methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance
5 with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

10 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,
15 including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally
20 provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another
25 amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be
30 expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays

for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured
5 by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter
10 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node
15 cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic
20 cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature*
25 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols*
30 *in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient
5 by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic
10 acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function
15 (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides.
20 For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used
25 to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II
30 molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

- 10 The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bowman et al., *J. Virology* 61:1992-1998; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnoli et al., *Cellular Immunology* 133:327-341, 1991; Brown et al., *J. Immunol.* 153:3079-3092, 1994.

25 Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, *J. Immunol.* 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*, J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

30 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those
5 described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj
10 et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz
15 et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and
20 development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

25 A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines,
30 thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of

5 hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or

10 *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

15 Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood

20 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of*

25 *Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359,

30 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

5 A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth
10 in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of
15 congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce
20 differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

25 Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and
30 other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce
5 differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in
10 the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve
15 tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present
20 invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of
25 non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac)
30 and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting
5 differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described
10 in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in:
Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year
15 Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related
20 activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals
25 and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example,
30 United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

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Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells.

- 10 Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses
- 15 against the tumor or infecting agent.

- A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population
- 20 of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

- Assays for chemotactic activity (which will identify proteins that induce or prevent
- 25 chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene
- 30 Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. *J. Clin. Invest.* 95:1370-1376, 1995; Lind et al. *APMIS* 103:140-146, 1995; Muller et al. *Eur. J. Immunol.* 25: 1744-1748; Gruber et al. *J. of Immunol.* 152:5860-5867, 1994; Johnston et al. *J. of Immunol.* 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

10 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 15 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

30 The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 5 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in 10 the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat 15 inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting 20 from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major 25 roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

30 The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

5 E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to
10 their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention
15 encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue
20 in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and
25 polynucleotides of the present invention encoding such proteins, can be used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the
30 cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides
5 encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

10 Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or
15 tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

20 Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height,
25 weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein,
30 carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen

5 in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

10 A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term

15 "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,

20 IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention,

25 or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

30 A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, 5 preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. 10 Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not 15 increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and 20 the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous 25 therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the 30 carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, *J. Amer.Chem.Soc.* 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, *FEBS Lett.* 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal

antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting
5 and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When
10 administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also
15 optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the
20 developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular
25 application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins
30 or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-

aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns.

- 5 In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

- 10 A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-
methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl
15 polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

- 20 In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

- 25 The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

- The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering
30 various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline
5 labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without
10 limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

15 Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Merberg, David
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael J.
- (ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES
ENCODING THEM
- (iii) NUMBER OF SEQUENCES: 28
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Genetics Institute, Inc.
 - (B) STREET: 87 CambridgePark Drive
 - (C) CITY: Cambridge
 - (D) STATE: MA
 - (E) COUNTRY: U.S.A.
 - (F) ZIP: 02140
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
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 - (B) REGISTRATION NUMBER: 41,323
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(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 719 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```

GCTGTTTGTA TTTTGGCTGC TGCAGGAGCC ATTTTAGAAA TAAATATCTT CCTTCAATAG      60
ATGAAAATGA AAATACAGAA AAAAGAGAAG CAGTTGTCAA ATTTAAAAGT TTTGAATCAC      120
TCCCCAATGT CTGATGCCTC TGTCAATTTT GACTACAAAT CTCCATCCCC ATTTGACTGC      180
AGCACTGATC AAGAAGAGAA AATTGAAGAT GTTGCTAGTC ACTGTCTGCC TCAGAAGGAC      240
CTGTATACTG CTGAAGAGGA AGCTGCTACC CTTTTCCTA GGAAAATGAC ATCCCATAAT      300
GGGATGGAGG ACAGTGGAGG AGGAGGTACT GGAGTGAAGA AGAAACGGAA GAAAAAGGAG      360
CCAGGAGACC AAGAGGGTGC AGCAAAGGGA AGCAAGGACA GAGAGCCCAA GCCAAAGAGG      420
AAACGAGAAC CGAAAGAGCC AAAGGAACCC AGAAAGGCCA AGGAGCCGAA GAAGGCCAAG      480
GAGCACAAGG AGCCGAAGCA AAAAGATGGG GCAAAGAAGG CACGGAAGCC CCGGGAGGCC      540
TCGGGCACCA AGGAGGCCAA AGAGAAGAGG AGCTGCACTG ACTCTGCAGC CAGGACGAAG      600
TCCAGGAAGG CCAGCAAGGA GCAAGGACCA ACCCCAGTGG AAAAAAAAAA AAAAAAAAAA      660
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA      719

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 194 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Met Lys Met Lys Ile Gln Lys Lys Glu Lys Gln Leu Ser Asn Leu Lys
1           5           10          15
Val Leu Asn His Ser Pro Met Ser Asp Ala Ser Val Asn Phe Asp Tyr
20          25          30
Lys Ser Pro Ser Pro Phe Asp Cys Ser Thr Asp Gln Glu Glu Lys Ile
35          40          45

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Glu Asp Val Ala Ser His Cys Leu Pro Gln Lys Asp Leu Tyr Thr Ala
 50 55 60
 Glu Glu Glu Ala Ala Thr Leu Phe Pro Arg Lys Met Thr Ser His Asn
 65 70 75 80
 Gly Met Glu Asp Ser Gly Gly Gly Gly Thr Gly Val Lys Lys Lys Arg
 85 90 95
 Lys Lys Lys Glu Pro Gly Asp Gln Glu Gly Ala Ala Lys Gly Ser Lys
 100 105 110
 Asp Arg Glu Pro Lys Pro Lys Arg Lys Arg Glu Pro Lys Glu Pro Lys
 115 120 125
 Glu Pro Arg Lys Ala Lys Glu Pro Lys Lys Ala Lys Glu His Lys Glu
 130 135 140
 Pro Lys Gln Lys Asp Gly Ala Lys Lys Ala Arg Lys Pro Arg Glu Ala
 145 150 155 160
 Ser Gly Thr Lys Glu Ala Lys Glu Lys Arg Ser Cys Thr Asp Ser Ala
 165 170 175
 Ala Arg Thr Lys Ser Arg Lys Ala Ser Lys Glu Gln Gly Pro Thr Pro
 180 185 190
 Val Glu

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2584 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGTGATTCTC CTGCCTCAGC CTCCCGAGTA GGTGGGATTA TAGGCATGTG CCACTGTGCC 60
 CGGTTTATTT TTGTATTTTT AATAGAAATG GGGTTTCACC AGGCTGGTCT TGAACCTCTG 120
 ACCTCAAGTG ATCCACCCGC CTCAGCCTCT CAAGGGACTA GGATTACAGG CAAGAGCCAC 180
 TGGCCTGGC CTCTTTTAAC CATTTTGAAT TGACTTTTGT GGATGGGGTA AGATAAGGGT 240
 CCAATTTTCAT TTCTTGGCAT GTGGTTATCT AGCTTTTCA ACACCATTTA TTAAAGAGAC 300

TATCCTTTCT TTATTGTGTA CTTTGTGACAC CTTTGTGAT GATTAGTTGG CCACATAAAC	360
GAGGATTTAT TTCTGGGATT CCTATTCTGT TCCATTGGTC TATATGTCTC CTTTATGCC	420
AGTACCATAC AGTTTTGATT ACTGTAGGTC TGTAATATAA TTTGAAATGA AGTGTGATGC	480
CACCAGCTTT GTTCTTCTTG CTCAGGATCA TTTTAGATAT TCTGGGTCTT TTGGGTCTG	540
TATGGATGTT AGGAATTTTT TTTTFTTTC TGTGAAAAAT GTCATTGGAG TTTTGCTAGA	600
GATTGCGTTG AATCTGTAGA CTACTTGTG TATTGCAGAC ATTTTGACAA TAATGATTCT	660
TCTGATCCTG AACATGGGAT AGCTTCCAT TTATTGTGT CATCTCCAGT TCTTTCATAT	720
ATGTATTATA GCTTTTAGCA TACACATCTT TCCCCTCCTT GGTAACCTT ATTCCTAAGT	780
ATTTTATTCC TTTTGATGCT ATTGTAAATG GGATTGCTT CTTAATTTCT TTCTTGATA	840
CTTCACTGTT AGTGAAGTGT AATTGATTTT TGTATGTTGA TTTTGTATCC TGAAACTTTA	900
CTGGATTCGT TTATTCATTC TAACAGTTTT TAGTGGCATA TTTAGGGTTT TCTGTATATA	960
GGATGATGTC ACCTGCAGAG ACAATTTTAC TTCTTCCTTT CTGATTGGA TGCCTTTTAT	1020
TTCTTTTCTT TGCCTAATTT CTGTGGCTAG GATTCTAGT ACTATGTTGA ATGTAAGTGA	1080
TAAGTGTGGG CATCCTTGTC TGTCTTGTC ACATTCAGTT GTATGTGCAA TACTGGAACC	1140
ATCCAGCTCA TAGTCACGTA ATTCCTCTTT GTGCAGCTC ATGTAAATC ACACCCCTAT	1200
TCACATTTTT TTCTGTCTGT CTCCCACCTC TCCAGTCCC TGCCCTGCAA CTTTCAGTTA	1260
CTTCAGACTC TCAGAAGACT AGCCTCTAAA TACCTCAATT TATCTGCACT ACTGTGGTCT	1320
ACTTGAAATT CTCTTCCCTC TTCTGCAGTT TGTAATGGCA TTCAGGCCAA AACTGTAGT	1380
AGTTTTAGGG CTCTCTTCAT TTGCTTCTCT GCTCCTAGGG ATCATAGTGC TGTGCTATCT	1440
GTTGTCCAGC ATCTGACACA GTTGGTTTTA TATTTTGTCT GGTTTTCTAG TTATTAAGCA	1500
GGTTAAGTCT GGTTCCTGCT GTTCTATATA GCAGGAAGCA AAGGTTCTCT CATGAATTTT	1560
TAGCATAATA ACATAAGCGT GGATTCCAAA AATTCAATAC ACAGATCCTG GAAATCTGTT	1620
TACTATGTTT TATACATTCT GTGAAAGCTG GAGAATATAT ATTTGTTTTA CTATGTGTAT	1680
CGCAAATAAA ATATCAATTT CATGTGCCAG AGAATTGAAT ACATTATCAA AGGGTCATTT	1740
CATAACGTTA TAATCACCAT CCATCCTGTA AGTCCTTTGA AATTTCTTCT TTTCTATGGA	1800
TCTAACATTG ATCAATAACG AATTCCTAAG CATCTATATT AGTTAGCCCA GTGTTTCTCA	1860
AAGTCCACCG CATGTAAAAA TCATCTAGGG AATCTTTCTA AAATGTGGAT TCTGATTTAG	1920
TAGGTCTGGG GTGAGGTCTT CCCTTTTGCA ATTCCAGCAA GTTCCCATGG GATGCTGGTA	1980

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CTGGTTAATG AAGTCACTTA GAGTAGCAAG GAGCCTGTTT GCCTAGTATT TACAATGAGC   2040
ACGTTTTGGG TATCATCAAA ACAAGAGAAT CTAAAAATGT ATGGTGTGGG TGGAAGGTTG   2100
TGTTACTTGA TATTTCAAAA AGATCATTGA AATCAGAAAA TCTCAGAGAT ATGTTGGATT   2160
TCATCACATT TATTCTATGG CTTAATGTTG TTTTATTTTG AATATATAAT AAGAGAGATA   2220
CCACAAATCT TTAGCTATTA ATATTTAGGG ATGTTAATGT CCTTAATTCA TATTGTCTCA   2280
AATGTGATTC ATTCCCTCTA TAGGTATACT AAAACAGGCA TTCATGCCTA CAAAACCATC   2340
TTCCTAACTT TCTTTCCTCT TTTTAGTCTC TTCCTGAACC AGTGACAGTG GTTCTCAAAC   2400
ATTTTGGTCT GAGGACCCCT TTATGGCCTT AAAAATGATC GAAGAGCTTT TATTTATGAA   2460
GGTAATACCT GCTAATACTT GTTGTAATCT ATTAACATTG AGAAATGTAA AAATTTTTAT   2520
TAATTCACCT AAAATATCAA TAAACCCATT ATTTGCTAAT AAAAAAAAAA AAAAAAAAAA   2580
AAAA                                              2584

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Met Phe Tyr Thr Phe Cys Glu Ser Trp Arg Ile Tyr Ile Cys Phe Thr
1           5           10           15

Met Cys Ile Ala Asn Lys Ile Ser Ile Ser Cys Ala Arg Glu Leu Asn
          20           25           30

Thr Leu Ser Lys Gly His Phe Ile Thr Leu
          35           40

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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2233 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTTCCCATC TTTGCAAAG AAAC TTTTGA TCTCTCTGTG CAAAGATGTT CCCTTTCAAG	60
TTAAGTGTGT GGCCTGCCAC AAGACACTGC GTTCCCACAT GGAGCTCACT GCCCATTTCA	120
GAGTTCATTG TCGAAATGCT GGACCTGTAG CTGTAGCTGA GAAGAGCATT ACCCAGGTTG	180
CAGAGAAATT CATATTAAGA GGT TATTGTC CAGATTGCAA TCAAGTCTTT GTGGATGAAA	240
CCAGCACCCA AAATCATAAG CAGAATTCAG GACACAAAGT CCGAGTCATT AACTCAGTGG	300
AAGAATCAGT CTTACTCTAT TGCCACAGCA GCGAAGGGAA CAAGGATCCT TCTTCTGACT	360
TGCATTTATT GTTGGATCAA TCAAAATTTT CATCACTTAA AAGAACCATG TCTATTAAAG	420
AATCTAGCTC ACTGGAGTGC ATTGCCATTTC CAAAAAGAA GATGAATTTA AAAGATAAAA	480
GCCATGAAGG TGTGCTTGT GTCCAGAAAG AAAAATCAGT AGTTAAAACC TGGTTCGTG	540
AATGCAATCA GCGATTCCCA AGTGAAGATG CAGTAGAAAA GCATGTTTTC TCAGCAAACA	600
CAATGGGTTA TAAATGTGTG GTCTGTGGAA AGGTATGTGA TGATT CAGGG GTCAATCGTT	660
TACACATGAG CCGGATTCAC GGAGGGGCAC ATTTAAATAA CTTTCTTTTC TGGTGTGCGA	720
CATGCAAAAA GGAGTTAACA AGGAAAGATA CTATCATGGC ACATGTGACT GAATTT CATA	780
ATGGACACAG ATATTTTTAT GAGATGGATG AGGTAGAAGG TGAAACTTTG CCATCATCCT	840
CTACAACATT GGATAATTG ACTGCTAACA AGCCTTCATC AGCTATTACT GTTATTGATC	900
ATTCCCCGGC AAATAGTTCT CCGAGGGGTA AATGGCAATG CCGGATTTGT GAAGATATGT	960
TTGATTCCCA GGAATATGTA AACAGCACTG CATGCTTTTG GCAAGCCACA AGTTTCATAG	1020
ATACAGCTGT GCTCACTGCA GAAAGCCTTT TCATAAGATA GAAACATTGT ACCGACATTG	1080
CCAAGATGAG CATGACAATG AGATAAAGAT TAAATACTTC TGTGGGCTTT GTGATCTTAT	1140
CTTTAATGTG GAAGAAGCAT TTTTGAGTCA TTATGAGGAG CACCACAGCA TAGATTATGT	1200
ATTTGTGTCA GAAAAAACTG AAAC TTCAAT TAAACCGAA GATGATTTTC CAGTAATAGA	1260
GACCAGTAAC CAGTTAACTT GTGGTTGCCG TGAGAGTTAC ATCTGTAAAG TCAACAGAAA	1320
AGAAGATTAT AGCAGATGTC TCCAAATCAT GCTGGATAAA GGAAAACTGT GGTTCGCTG	1380
CAGTTTATGT TCGGCAACAG CACAGAATTT AACCGACATG AACACTCATA TCCATCAAGT	1440
GCACAAAGAA AAGAGTGATG AGGAGGAGCA GCAGTATGTA ATCAAGTGTG GCACCTGCAC	1500

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CAAAGCATTT CATGATCCTG AGAGTGCACA GCAGCATTTT CATAGAAAAC ATTGCTTCTT 1560
ACAGAAACCC AGTGTGGCTC ATTTTGGATC TGAAAAATCA AACCTGTACA AGTTTACTGC 1620
TAGTGCCTCA CATAAGAGA GAAAACTGAA ACAGGCAATA AACTATTCAA AAAGTTTAGA 1680
CATGGAGAAA GGAGTTGAGA ATGACCTAAG CTATCAGAAT ATAGAGGAAG AAATGTTGA 1740
GCTTCCAGAT TTGGATTACC TCGAACCAT GACTCATATA GTCTTTGTAG ATTTTGATAA 1800
CTGGTCAAAC TTTTTTGGTC ATCTACCAGG GCATCTAAAC CAAGGAACAT TTATTTGGGG 1860
CTTTCAAGGT ACGGTTAATA AGAAAAACAA AAGAAAACCT TTTCCACCT CTTAGAATAT 1920
AGTTCAGTTT AAAAGGCTCC TCTTAAACCT TCCTGGATAG AACATAGGAA CATAATTGGA 1980
ATATGTGTTCT TTGTATTAT AGTTACTCTG CTAGAATCGT TTTCTTTACA TGCCTCTGTG 2040
GTAAATGTTA GCTCTATCTG GTGACTCAAA GTTTATGGAT CTTTGGCCG GCGCGGTGG 2100
CTCAGTCTG TAATCCAGA ACTTTGAAG GCTGAGCGG ACGGATCACG AGGTCAGAAG 2160
ATCGAGACCA TCCTGGCTAA CATGGTGAAA CCCCCTCTCT ACTAAAAAAA AAAAAAAAAA 2220
AAAAAAAAA AAA 2233

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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 320 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```

Met Glu Leu Thr Ala His Phe Arg Val His Cys Arg Asn Ala Gly Pro
1      5      10      15
Val Ala Val Ala Glu Lys Ser Ile Thr Gln Val Ala Glu Lys Phe Ile
20     25     30
Leu Arg Gly Tyr Cys Pro Asp Cys Asn Gln Val Phe Val Asp Glu Thr
35     40     45
Ser Thr Gln Asn His Lys Gln Asn Ser Gly His Lys Val Arg Val Ile
50     55     60
Asn Ser Val Glu Glu Ser Val Leu Leu Tyr Cys His Ser Ser Glu Gly
65     70     75     80

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Asn Lys Asp Pro Ser Ser Asp Leu His Leu Leu Leu Asp Gln Ser Lys
      85                      90                      95

Phe Ser Ser Leu Lys Arg Thr Met Ser Ile Lys Glu Ser Ser Ser Leu
      100                    105                    110

Glu Cys Ile Ala Ile Pro Lys Lys Lys Met Asn Leu Lys Asp Lys Ser
      115                    120                    125

His Glu Gly Val Ala Cys Val Gln Lys Glu Lys Ser Val Val Lys Thr
      130                    135                    140

Trp Phe Cys Glu Cys Asn Gln Arg Phe Pro Ser Glu Asp Ala Val Glu
      145                    150                    155                    160

Lys His Val Phe Ser Ala Asn Thr Met Gly Tyr Lys Cys Val Val Cys
      165                    170                    175

Gly Lys Val Cys Asp Asp Ser Gly Val Ile Arg Leu His Met Ser Arg
      180                    185                    190

Ile His Gly Gly Ala His Leu Asn Asn Phe Leu Phe Trp Cys Arg Thr
      195                    200                    205

Cys Lys Lys Glu Leu Thr Arg Lys Asp Thr Ile Met Ala His Val Thr
      210                    215                    220

Glu Phe His Asn Gly His Arg Tyr Phe Tyr Glu Met Asp Glu Val Glu
      225                    230                    235                    240

Gly Glu Thr Leu Pro Ser Ser Ser Thr Thr Leu Asp Asn Leu Thr Ala
      245                    250                    255

Asn Lys Pro Ser Ser Ala Ile Thr Val Ile Asp His Ser Pro Ala Asn
      260                    265                    270

Ser Ser Pro Arg Gly Lys Trp Gln Cys Arg Ile Cys Glu Asp Met Phe
      275                    280                    285

Asp Ser Gln Glu Tyr Val Asn Ser Thr Ala Cys Leu Trp Gln Ala Thr
      290                    295                    300

Ser Phe Ile Asp Thr Ala Val Leu Thr Ala Glu Ser Leu Phe Ile Arg
      305                    310                    315                    320

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(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1285 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGAAAGCCAT TTCTAGCACA GAAGCAGTTC TAAACAACCG ATTCATTCTGA GTCTTGTGGC	60
ATAGGGAAAA TAATGAGCAA CCGACACTAC AGTCCTCAGC ACAGCTGCTC CTGCAACAAC	120
AGCAAACACT TAGTCACCTC TCACAGCAGC ACCATCACCT GCCACAGCAT CTACATCAGC	180
AGCAGGTGCT AGTGGCCCAG TCTGCTCCTT CAACAGTGCA CGGAGGTATC CAGAAGATGA	240
TGAGCAAACC ACAGACATCA GGTGCATATG TTCTTAACAA AGTTCCTGTT AAACATCGTC	300
TTGGACATGC AGGTGGTGCT GGAGAAGATT GCCAGATATT TTCAACTCCA GGCCATCCAA	360
AAATGATTTA CAGCTCCTCA AACTTAAAGA CACCTTCAAA GCTCTGTTCA GGGTCTAAAT	420
CTCATGATGT TCAAGAAGTG CTTAAAAAAA AACAGGAAGC AATGAAGTTA CAACAAGATA	480
TGAGGAAAAA AAGACAGGAA GTGTTAGAAA AGCAAATAGA ATGCCAAAAG ATGTTAATAT	540
CCAAGTTAGA AAAAAACAAA AACATGAAAC CAGAAGAAAG AGCAAATATA ATGAAGACTT	600
TGAAAGAGCT TGGAGAGAAG ATCTCACAAT TAAAGATGA ATTAAAAACA TCTTCTGCAG	660
TCTCCACACC ATCTAAAGTG AAGACAAAAA CGGAGGCCCA GAAGGAGTTA TTAGATACTG	720
AACTGGACCT CCACAAGAGG CTGTCCTCAG GAGAAGACAC CACAGAATTA CGGAAAAAAC	780
TCAGTCAGTT ACAGGTTGAG GCTGCACGGT TAGGTATTTT ACCTGTGGGT CGAGGAAAGA	840
CCATGTCTC TCAAGGTCGA GGAAGAGGCC GAGGGCGTGG AGGAAGAGGA AGGGGCTCAC	900
TAAATCACAT GGTGGTGGAC CATCGTCCCA AAGCACTAAC AGTTGGAGGA TTCATTGAGG	960
AAGAAAAAGA AGACTTGCTT CAGCATTTCT CAACCGCAA CCAAGGGCCA AAATTTAAAG	1020
ACCGTCGGCT ACAGATATCA TGGCACAAGC CCAAGGTACC ATCTATATCC ACTGAGACTG	1080
AAGAAGAAGA AGTCAAGGAG GAGGAAACAG AAACCTCAGA TTTGTTTTTG CCTGATGATG	1140
ACGATGAAGA TGAAGATGAA TATGAGTCTC GCTCATGGCG AAGATGAAAT CTGATGCTAG	1200
CTGTATAATT TTTAGGAATA TTGTTTAGAA GAACAACTTT TAAAAATTAT TTAAAAGAAG	1260
TCAATGAGCC AAAAAAAAAA AAAAA	1285

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 316 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

Met Met Ser Lys Pro Gln Thr Ser Gly Ala Tyr Val Leu Asn Lys Val
1           5           10           15

Pro Val Lys His Arg Leu Gly His Ala Gly Gly Ala Gly Glu Asp Cys
          20           25           30

Gln Ile Phe Ser Thr Pro Gly His Pro Lys Met Ile Tyr Ser Ser Ser
          35           40           45

Asn Leu Lys Thr Pro Ser Lys Leu Cys Ser Gly Ser Lys Ser His Asp
          50           55           60

Val Gln Glu Val Leu Lys Lys Lys Gln Glu Ala Met Lys Leu Gln Gln
65           70           75           80

Asp Met Arg Lys Lys Arg Gln Glu Val Leu Glu Lys Gln Ile Glu Cys
          85           90           95

Gln Lys Met Leu Ile Ser Lys Leu Glu Lys Asn Lys Asn Met Lys Pro
          100          105          110

Glu Glu Arg Ala Asn Ile Met Lys Thr Leu Lys Glu Leu Gly Glu Lys
          115          120          125

Ile Ser Gln Leu Lys Asp Glu Leu Lys Thr Ser Ser Ala Val Ser Thr
          130          135          140

Pro Ser Lys Val Lys Thr Lys Thr Glu Ala Gln Lys Glu Leu Leu Asp
145          150          155          160

Thr Glu Leu Asp Leu His Lys Arg Leu Ser Ser Gly Glu Asp Thr Thr
          165          170          175

Glu Leu Arg Lys Lys Leu Ser Gln Leu Gln Val Glu Ala Ala Arg Leu
          180          185          190

Gly Ile Leu Pro Val Gly Arg Gly Lys Thr Met Ser Ser Gln Gly Arg
          195          200          205

Gly Arg Gly Arg Gly Arg Gly Gly Arg Gly Arg Gly Ser Leu Asn His
210          215          220

Met Val Val Asp His Arg Pro Lys Ala Leu Thr Val Gly Gly Phe Ile
225          230          235          240

Glu Glu Glu Lys Glu Asp Leu Leu Gln His Phe Ser Thr Ala Asn Gln

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	245		250		255										
Gly	Pro	Lys	Phe	Lys	Asp	Arg	Arg	Leu	Gln	Ile	Ser	Trp	His	Lys	Pro
			260					265					270		
Lys	Val	Pro	Ser	Ile	Ser	Thr	Glu	Thr	Glu	Glu	Glu	Glu	Val	Lys	Glu
			275				280						285		
Glu	Glu	Thr	Glu	Thr	Ser	Asp	Leu	Phe	Leu	Pro	Asp	Asp	Asp	Asp	Glu
			290				295					300			
Asp	Glu	Asp	Glu	Tyr	Glu	Ser	Arg	Ser	Trp	Arg	Arg				
305						310					315				

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2346 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CACGCGAGGC GCTGTCTTT CAGCACCACA AGCTCGGGCT GAGGAGGGAG GACTCCTGGC	60
CGTCTCTCTC CTCTTCAAAT TGGCTTGAAT CTGCTCTGAC CCCCCACGAG TGCAGCACAG	120
TCTGGGAAGA AAGGCGTAAG GATGGTGAAG CTGAACAGTA ACCCCAGCGA GAAGGGAACC	180
AAGCCGCCTT CAGTTGAGGA TGGCTTCCAG ACCGTCCCTC TCATCACTCC CTTGGAGGTT	240
AATCACTTAC AGCTGCCTGC TCCAGAAAAG GTGATTGTGA AGACAAGAAC GGAATATCAG	300
CCGGAACAGA AGAACAAAGG GAAGTTCCGG GTGCCGAAAA TCGCTGAATT TACGGTCACC	360
ATCCTTGTC A GCCTGGCCCT AGCTTTCTCT GCGTGCATCG TGTTCTGGT GGTTTACAAA	420
GCCTTCACCT ATGATCACAG CTGCCCAGAG GGAATTCGTCT ATAAGCACAA ACGCTGTATC	480
CCAGCCTCCC TGGATGCTTA CTACTCTCC CAGGACCCCA ATTCCAGAAG CCGCTTCTAC	540
ACAGTCATCA GCCACTACAG CGTGGCCAAG CAGAGCACTG CCCGGGCCAT CGGGCCGTGG	600
CTGTCAGCAG CCGCTGTCT CCATGAGCCC AAGCCGCCCA AGAACCAGG GCCACTAAAG	660
GCCTGCCCCA GCCAAAATGG GGGGCGGGGT GGAAAGGAGG ACCCCATTG GCTAACCCTA	720
GCTCCAGTTA CAAAACAACA CTGTACTCCT GGGATATGGG GGCAGGGGCG GGCAGGGCA	780

GGGTGGGGG AAAAACGCAC CAAAAACGTG GTGTGTGCTG GAGTTGTCTG AACCGATATT	840
TCTTTTGTGTT CCTTGGTATT GTTGATTTCGT CGCCGAGTCA GGCTCATGTA CAAAGGCATG	900
TTTCGTGTTG ATTGTTCCCA TGTAAGATAT TTTTAAAGCC ACTGCTTATT CTTTGTTAGG	960
AAAATGTAAC AGCAGAAAAG GAAAGAAACA AAGAACATGA AAAAAAGCA TTAAACTGGC	1020
TCCATCAGAA GACGTTGAAG GGCAGTGAAG AGCACAGACT CTGTGGGCTT CTTAGATAAG	1080
AAAACGTAGC TTCAGTGGG GCTCCAGGGT TGCAGAGTAT GAGTGACACA GACCGGGACT	1140
ATTCCATTAG CCTGTGGTCT GCAGGGTAGG CCCGCAGGAA ATGAGGAATG GCCGAGCTGG	1200
AGAGAAGAGC TGATTTTGGC ATTACTAAGC CCAGAACGCA CATAACCCAT AGTGAAATGT	1260
GCTGGCCTCT GGTGCATTTT GCAAGATGAG CACAACTTT CTGGGCCTCC ATCCTAGGAC	1320
CTGGGCAGAC CCACATGGCC TGGGCTTTGA ATGCCACCC TGCACGGTG GGTTTTGCAT	1380
CAGCAAACGC TGAGGAGTGG GCAGATTTTT TTTGTTTTT GCTTGCATTT TTTAGATCCA	1440
CACCTGGATA CTGCCCATGT TGACGAGACA GCAGCAGGGG GAGAGGGAGG GAAGGAAGGT	1500
GCGGCTGCAA GAAGGAAGGC ACGGGACAGG CATGTGACAC TAGGCCACAA GCGATAAGCA	1560
CAGGCACCTG ACTTTTAAGT TTTTGTGTGT TGTGTGTTT CCAAAGTGCT GATAACAATA	1620
ACAACAACAA TAGGATTCCA ACCAGGAGCC TCAAGTGACA GCCAGGAAGA GACCTGAAGG	1680
TTGGGGCCAC CACAATGCCA AATCGTTTCT AAAGGAAGCT GAAAAATGGG ACTGTCTTTT	1740
GCCCACTTCG TTGTGTTAAA AGGGGACATT TGTCCAACT CCCCAACCGA GTTTTAGAAG	1800
CTCCTGACAA GGAGGCAGCA TCCAGCCTTG ACCAGGCCTC CCAGTTCCCT GGAACCGTAT	1860
CAGGCATTCT CCTGCCTCTC ACAAATGTTT CAGGGAGGCC AGTTCTGCAG GGTGTCAGCT	1920
CCAGGACCCA CAGGGCCAGA ACCAGCTGGG AGAATTGGTT ATTTGAGATG TGGTACTGCT	1980
TCCTCACAAG TCTCCACAG GCCATGTAAA GGGTATTTTT TTGTGGCTTG CTGTGTTGCT	2040
GAGATCATCG TATGCAACAG CTGGGTAATA AGACTAGCAT AGCTCAAAC ATCCTGCCAA	2100
ACGCTCTCAT ATGATTTTTT CTCCCTTCTC CCCCAACCTC CAATCACCTT GAGTCACCTG	2160
TAAATTTCATT TGTCAATCAA AGCGGAATAA CAAGTTGTCC CTAGCAAAAC CGCTGAGCGC	2220
TTTATAATTT TGTGGTGTAT TTTTGTGAGT AGGTAGCAGA GGCGGAAGTA TTTTTTGGTG	2280
TAATTCCTGA AATTTTCTGA CAGGAAACAA ATAAAGATAG ATGTGTCTGA GAAAAA	2340
AAAAA	2346

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 229 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met	Val	Lys	Leu	Asn	Ser	Asn	Pro	Ser	Glu	Lys	Gly	Thr	Lys	Pro	Pro	1	5	10	15
Ser	Val	Glu	Asp	Gly	Phe	Gln	Thr	Val	Pro	Leu	Ile	Thr	Pro	Leu	Glu	20	25	30	
Val	Asn	His	Leu	Gln	Leu	Pro	Ala	Pro	Glu	Lys	Val	Ile	Val	Lys	Thr	35	40	45	
Arg	Thr	Glu	Tyr	Gln	Pro	Glu	Gln	Lys	Asn	Lys	Gly	Lys	Phe	Arg	Val	50	55	60	
Pro	Lys	Ile	Ala	Glu	Phe	Thr	Val	Thr	Ile	Leu	Val	Ser	Leu	Ala	Leu	65	70	75	80
Ala	Phe	Leu	Ala	Cys	Ile	Val	Phe	Leu	Val	Val	Tyr	Lys	Ala	Phe	Thr	85	90	95	
Tyr	Asp	His	Ser	Cys	Pro	Glu	Gly	Phe	Val	Tyr	Lys	His	Lys	Arg	Cys	100	105	110	
Ile	Pro	Ala	Ser	Leu	Asp	Ala	Tyr	Tyr	Ser	Ser	Gln	Asp	Pro	Asn	Ser	115	120	125	
Arg	Ser	Arg	Phe	Tyr	Thr	Val	Ile	Ser	His	Tyr	Ser	Val	Ala	Lys	Gln	130	135	140	
Ser	Thr	Ala	Arg	Ala	Ile	Gly	Pro	Trp	Leu	Ser	Ala	Ala	Ala	Val	Ile	145	150	155	160
His	Glu	Pro	Lys	Pro	Pro	Lys	Asn	Pro	Gly	Pro	Leu	Lys	Ala	Cys	Pro	165	170	175	
Ser	Gln	Asn	Gly	Gly	Arg	Gly	Gly	Lys	Glu	Asp	Pro	His	Trp	Leu	Thr	180	185	190	
Gln	Ala	Pro	Val	Thr	Lys	Gln	His	Cys	Thr	Pro	Gly	Ile	Trp	Gly	Arg	195	200	205	
Gly	Arg	Gly	Arg	Ala	Gly	Trp	Gly	Glu	Lys	Arg	Thr	Lys	Asn	Val	Val	210	215	220	

Cys Ala Gly Val Val
225

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2104 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGATGAGTCT CAAGATGGAC AACCGGGATG TTGCAGGAAA GGCTAACCGG TGGTTTGGGG	60
TTGCTCCCCC TAAATCTGGA AAAATGAACA TGAACATCCT TCACCAGGAA GAGCTCATCG	120
CTCAGAAGAA ACGGGAAATT GAAGCCAAAA TGGAACAGAA AGCCAAGCAG AATCAGGTGG	180
CCAGCCCTCA GCCCCACAT CCTGGCGAAA TCACAAATGC ACACAACTCT TCCTGCATTT	240
CCAACAAGTT TGCCAACGAT GGTAGCTTCT TGCAGCAGTT TC'TGAAGTTG CAGAAGGCAC	300
AGACCAGCAC AGACGCCCCG ACCAGTGCGC CCAGCGCCCC TCCCAGCACA CCCACCCCCA	360
GCGCTGGGAA GAGGTCCCTG CTCATCAGCA GCGCGACAGG CCTGGGGCTG GCCAGCCTGC	420
CGGGCCCTGT GAAGAGCTAC TCCCACGCCA AGCAGCTGCC CGTGGCGCAC CGCCCGAGTG	480
TCTTCCAGTC CCCTGACGAG GACGAGGAGG AGGACTATGA GCAGTGGCTG GAGATCAAAG	540
TTTACCCCC AGAGGGAGCC GAGACTCGGA AAGTGATAGA GAAATTGGCC CGCTTTGTGG	600
CAGAAGGAGG CCCCAGTTA GAAAAAGTAG CTATGGAGGA CTACAAGGAT AATCCAGCAT	660
TTGCATTTTT GCACGATAAG AATAGCAGGG GATTCTCTA CTACAGGAAG AAGGTGGCTG	720
AGATAAGAAA GGAAGCACAG AAGTCGCAGG CAGCCTCTCA GAAAGTTTCA CCCCAGAGG	780
ACGAAGAGGT CAAGAACCTT GCAGAAAAGT TGGCCAGGTT CATAGCGGAC GGGGGTCCCG	840
AGGTGGAAAC CATTGCCCTC CAGAACAACC GTGAGAACCA GGCATTTCAGC TTTCTGTATG	900
AGCCCAATAG CCAAGGTAC AAGTACTACC GACAGAAGCT GGAGGAGTTC CGGAAAGCCA	960
AGGCCAGCTC CACAGGCAGC TTCACAGCAC CTGATCCCGG CCTGAAGCGC AAGTCCCCTC	1020
CTGAGGCCCT GTCAGGGTCC TTACCCCCAG CCACCACCTG CCCCGCCTCG TCCACGCCTG	1080
CGCCCACTAT CATCCCTGCT CCAGCTGCCC CCGGAAGCC AGCCTCCGCA GCCACCGTGA	1140

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AGAGGAAGCG GAAGAGCCGG TGGGGGCCTG AAGAGGATAA GGTAGAGCTC CCACCTGCTG      1200
AACTGGTGCA GAGGGACGTG GATGCCCTCTC CCTCGCCTCT GTCAGTTCAG GACCTCAAGG      1260
GGCTCGGCTA TGAGAAGGGG AAGCCTGTGG GTCTAGTGGG CGTCACAGAG CTTTCAGACG      1320
CCCAGAAGAA GCAGCTGAAG GAGCAGCAGG AGATGCAGCA GATGTACGAC ATGATCATGC      1380
AGCACAAGCG GGCCATGCAG GACATGCAGC TGCTGTGGGA GAAGGCAGTC CAACAGCACC      1440
AGCACGGCTA TGACAGTGAT GAGGAGGTGG ACAGCGAGCT GGGCACCTGG GAGCACCAGC      1500
TGCGGCGCAT GGAGATGGAT AAGACCAGGG AATGGGCCGA GCAGCTGACA AAGATGGGCC      1560
GGGGCAAGCA CTTTCATCGGA GACTTCCTGC CTCCAGACGA GCTGGAAAAG TTTATGGAGA      1620
CCTTCAAGGC CCTGAAGGAG GGCCGTGAGC CTGACTACTC AGAGTACAAG GAGTTCAAGC      1680
TGACTGTGGA GAACATCGGC TACCAGATGT TGATGAAGAT GGGCTGGAAG GAGGGCGAGG      1740
GGCTGGGCTC AGAGGGCCAG GGCATCAAGA ACCCAGTGAA CAAGGGCACC ACCACAGTGG      1800
ACGGCGCTGG CTTCGGCATT GACCGGCCGG CGGAGCTCTC CAAGGAGGAC GACGAGTATG      1860
AGGCGTTCCG CAAGAGGATG ATGCTGGCCT ACCGCTTCCG GCCCAACCCC CTGAACAATC      1920
CCAGACGGCC TTACTACTGA GTGTTCTGGA AATACATACT TTCTGAATGA CCAACCGTCC      1980
CTGGACTGTG GAATGTTCCG GCCTGCATTT CTGCCCACCC CTTCCGTTGT CACGAGTGCC      2040
GTGCCGTGTA ATAAAGTCCC AGTGCTCATC CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA      2100
AAAA                                             2104

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(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 645 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```

Met Ser Leu Lys Met Asp Asn Arg Asp Val Ala Gly Lys Ala Asn Arg
1           5           10           15

Trp Phe Gly Val Ala Pro Pro Lys Ser Gly Lys Met Asn Met Asn Ile
          20           25           30

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Leu His Gln Glu Glu Leu Ile Ala Gln Lys Lys Arg Glu Ile Glu Ala
 35 40 45
 Lys Met Glu Gln Lys Ala Lys Gln Asn Gln Val Ala Ser Pro Gln Pro
 50 55 60
 Pro His Pro Gly Glu Ile Thr Asn Ala His Asn Ser Ser Cys Ile Ser
 65 70 75 80
 Asn Lys Phe Ala Asn Asp Gly Ser Phe Leu Gln Gln Phe Leu Lys Leu
 85 90 95
 Gln Lys Ala Gln Thr Ser Thr Asp Ala Pro Thr Ser Ala Pro Ser Ala
 100 105 110
 Pro Pro Ser Thr Pro Thr Pro Ser Ala Gly Lys Arg Ser Leu Leu Ile
 115 120 125
 Ser Arg Arg Thr Gly Leu Gly Leu Ala Ser Leu Pro Gly Pro Val Lys
 130 135 140
 Ser Tyr Ser His Ala Lys Gln Leu Pro Val Ala His Arg Pro Ser Val
 145 150 155 160
 Phe Gln Ser Pro Asp Glu Asp Glu Glu Glu Asp Tyr Glu Gln Trp Leu
 165 170 175
 Glu Ile Lys Val Ser Pro Pro Glu Gly Ala Glu Thr Arg Lys Val Ile
 180 185 190
 Glu Lys Leu Ala Arg Phe Val Ala Glu Gly Gly Pro Glu Leu Glu Lys
 195 200 205
 Val Ala Met Glu Asp Tyr Lys Asp Asn Pro Ala Phe Ala Phe Leu His
 210 215 220
 Asp Lys Asn Ser Arg Gly Phe Leu Tyr Tyr Arg Lys Lys Val Ala Glu
 225 230 235 240
 Ile Arg Lys Glu Ala Gln Lys Ser Gln Ala Ala Ser Gln Lys Val Ser
 245 250 255
 Pro Pro Glu Asp Glu Glu Val Lys Asn Leu Ala Glu Lys Leu Ala Arg
 260 265 270
 Phe Ile Ala Asp Gly Gly Pro Glu Val Glu Thr Ile Ala Leu Gln Asn
 275 280 285
 Asn Arg Glu Asn Gln Ala Phe Ser Phe Leu Tyr Glu Pro Asn Ser Gln
 290 295 300
 Gly Tyr Lys Tyr Tyr Arg Gln Lys Leu Glu Glu Phe Arg Lys Ala Lys
 305 310 315 320
 Ala Ser Ser Thr Gly Ser Phe Thr Ala Pro Asp Pro Gly Leu Lys Arg

					325						330					335
Lys	Ser	Pro	Pro	Glu	Ala	Leu	Ser	Gly	Ser	Leu	Pro	Pro	Ala	Thr	Thr	
			340					345					350			
Cys	Pro	Ala	Ser	Ser	Thr	Pro	Ala	Pro	Thr	Ile	Ile	Pro	Ala	Pro	Ala	
		355					360					365				
Ala	Pro	Gly	Lys	Pro	Ala	Ser	Ala	Ala	Thr	Val	Lys	Arg	Lys	Arg	Lys	
		370				375					380					
Ser	Arg	Trp	Gly	Pro	Glu	Glu	Asp	Lys	Val	Glu	Leu	Pro	Pro	Ala	Glu	
385					390					395					400	
Leu	Val	Gln	Arg	Asp	Val	Asp	Ala	Ser	Pro	Ser	Pro	Leu	Ser	Val	Gln	
				405					410					415		
Asp	Leu	Lys	Gly	Leu	Gly	Tyr	Glu	Lys	Gly	Lys	Pro	Val	Gly	Leu	Val	
			420					425					430			
Gly	Val	Thr	Glu	Leu	Ser	Asp	Ala	Gln	Lys	Lys	Gln	Leu	Lys	Glu	Gln	
		435					440					445				
Gln	Glu	Met	Gln	Gln	Met	Tyr	Asp	Met	Ile	Met	Gln	His	Lys	Arg	Ala	
		450				455					460					
Met	Gln	Asp	Met	Gln	Leu	Leu	Trp	Glu	Lys	Ala	Val	Gln	Gln	His	Gln	
465					470				475						480	
His	Gly	Tyr	Asp	Ser	Asp	Glu	Glu	Val	Asp	Ser	Glu	Leu	Gly	Thr	Trp	
				485					490					495		
Glu	His	Gln	Leu	Arg	Arg	Met	Glu	Met	Asp	Lys	Thr	Arg	Glu	Trp	Ala	
			500					505					510			
Glu	Gln	Leu	Thr	Lys	Met	Gly	Arg	Gly	Lys	His	Phe	Ile	Gly	Asp	Phe	
		515					520					525				
Leu	Pro	Pro	Asp	Glu	Leu	Glu	Lys	Phe	Met	Glu	Thr	Phe	Lys	Ala	Leu	
		530				535					540					
Lys	Glu	Gly	Arg	Glu	Pro	Asp	Tyr	Ser	Glu	Tyr	Lys	Glu	Phe	Lys	Leu	
545					550				555						560	
Thr	Val	Glu	Asn	Ile	Gly	Tyr	Gln	Met	Leu	Met	Lys	Met	Gly	Trp	Lys	
			565					570						575		
Glu	Gly	Glu	Gly	Leu	Gly	Ser	Glu	Gly	Gln	Gly	Ile	Lys	Asn	Pro	Val	
			580					585					590			
Asn	Lys	Gly	Thr	Thr	Thr	Val	Asp	Gly	Ala	Gly	Phe	Gly	Ile	Asp	Arg	
		595					600					605				
Pro	Ala	Glu	Leu	Ser	Lys	Glu	Asp	Asp	Glu	Tyr	Glu	Ala	Phe	Arg	Lys	
		610				615					620					

Arg Met Met Leu Ala Tyr Arg Phe Arg Pro Asn Pro Leu Asn Asn Pro
625 630 635 640

Arg Arg Pro Tyr Tyr
645

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1642 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CAAGTTTTGT TGTGCTGATT TAACAGCCTG TGAATTCTGC AAACACGATC GTGAAAAAAT	60
GCCAATCTGT CCTGTGTAAG VCCTGTGTGA AGTTTGTACT TTAATCTACC AGATCACTCC	120
TTCACCCTCC ATAAAGATGT CTGAACCTGA CACTTCCTCA GGATTTTCGG GAAGTGTGGA	180
GAATGGAAC TTTCTTGAGC TGTPTCCAC ATCCCTGTCC ACGTCAGTGG ACCCATCCTC	240
AGGCCACCTG TCAAACGTCT ACATCTATGT GTCCATATTC CTCAGCCTTT TAGCGTTTCT	300
GCTTCTGCTT TTAATCATTG CCCTCCAGAG GCTCAAAAAT ATCATCTCCT CCAGTTCCTC	360
CTACCCAGAG TATCCAAGCG ACGCTGGAAG TTCTTTCACC AATTGGAAG TCTGCAGCAT	420
TTCTCTCAG AGGTCCACTT TTTCAAACCT TTCATCCTGA GGAAAATGGA AGAGTCCTTG	480
AGTGTGGCAG CAGTTTTGAC ATCCCCTTAC GGAAGTGTCC CGTGAGGCAT TGCCTCATGA	540
AAGAAATGAT CCTTTTGGTG TAGACCTGCT TCTCCTTCTC CTTTTTCTCT GATTTCTTTT	600
CTGTTTCATGA TGCTTTTCAT TTGGGGATGG AGACACCGAT GTTGGTGGAA ATGTGTGCAA	660
ACCCCAAGGT GCAGAATTTC ACACAAATGG CTTGATGAAT CTAGACTGGG CTTCTTCAGG	720
TAAGTCAGTT CATTCTACTT TGTGGACGC CGTAGACTCA TCTGAGGTGG CCTCTCCGTG	780
GATGCTGGAC ATGGACTCGC ACTTCATTTT TTTTACAAAG CCGTGAAATC AACTGAGCCT	840
GCAGAACTG GCAAAATCAA GTCTGACCTA TGTAGAAGTT ATTTTCCATA TTAAAAAGAT	900
AAAGTGGAGA CACCAAACCT AAAAAGGAAG AGAGTCAATT TAGATTTAAT GTATGACATT	960
TCTAAACTG AGGGTAAATA TATGCTAAAT ATTTTCTTTA ACTTCACTTT AACAAGTAAA	1020

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AATCACACTT ATTGATGAAT GTAAGTCATT TGGGAAAGTT TTGGAAGAGT TTACATTTTA 1080
ATAGCAAGAC AAACATGTAT TATGATGGAG CTTGTGATGT ATTTCTGCCT CCTGGAGTTT 1140
TATTTTGTTT TTCCTGCTTAT GTTTTAGTCA TAATGCCACA AAGTTGTGGA ATTTTGTGA 1200
TTAATTGCTG TTACTAGTAC TAAGAGAAGC ACCAGAAGAG ATGCCAAGAA GTTTTATAT 1260
GAATAATTTT TATCAGTGAG AATTAAGCAT ATGGAAAATA TTCAITTAGT TGTATTTTAT 1320
ACAGTAATAA CTCTTAGCTG TCGTGTAAGT TCCTTTATTC GGTTCATAG TCTTTATAAT 1380
TTTAGTGCAG AATTATATTA AGCCTCCAAG ATGTCTGATA TTTGTTCACT CACATTAGGT 1440
TGTAAGACTT AGAACTAAA TTGCAAATAT ATGTGTTATT ATATACTCCA CGAATGTTGC 1500
GTCTCTGATA ATTAGTTGTT GTATGTTAAC ATAATACTCT ACATTAGGAT TTCAGGATGT 1560
GAGTTTGAT TAAAAATTGT AGGCACTCCA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1620
AAAAAAAAA AAAAAAAAAA AA 1642

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(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 107 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```

Met Ser Glu Pro Asp Thr Ser Ser Gly Phe Ser Gly Ser Val Glu Asn
1           5           10           15

Gly Thr Phe Leu Glu Leu Phe Pro Thr Ser Leu Ser Thr Ser Val Asp
20       25       30

Pro Ser Ser Gly His Leu Ser Asn Val Tyr Ile Tyr Val Ser Ile Phe
35       40       45

Leu Ser Leu Leu Ala Phe Leu Leu Leu Leu Leu Ile Ile Ala Leu Gln
50       55       60

Arg Leu Lys Asn Ile Ile Ser Ser Ser Ser Tyr Pro Glu Tyr Pro
65       70       75       80

Ser Asp Ala Gly Ser Ser Phe Thr Asn Leu Glu Val Cys Ser Ile Ser
85       90       95

```


Ser Gln Arg Ser Thr Phe Ser Asn Leu Ser Ser
 100 105

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1365 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```

CGCAGGAAGC AGAAGAGCAG AGCGAGGACG ACGACGAGGA TACAGAAGAG GAACAGGGGG 60
AAGAAAAGGA AAAGGGAGCG CAGGAGAAAA GGAGGGGGAA GAGAGTCCGT TTTGCAGAAG 120
ATGAAGAAAA GAGTGAAAAT TCCTCGGAGG ACGGTGACAT AACGGATAAG AGTCTTTGTG 180
GAAGTGGTGA AAAGTACATC CCACCTCATG TGAGGCAAGC TGAGGAGACA GTGGACTTCA 240
AGAAAAAGGA AGAACTAGAA AGGCTGAAGA AACATGTAAA AGGTCTACTT AACAGGTTGA 300
GTGAACCCAA CATGGCTTCC ATCAGTGGGC AGCTGGAGGA ACTGTACATG GCCCAGCA 360
GAAAGGACAT GAATGACACC CTGACCTCCG CTCTCATGGG TGCCTGCGTC ACTGCCTCGG 420
CCATGCCCAG CAGACTGATG ATGGAGCATG TTCTCTTAGT CAGCATCCTT CACCACACAG 480
TTGGAATCGA GGTGGGTGCC CACTTTCTGG AGGCAGTGGT GAGGAAGTTC GATGCCATCT 540
ATAAATACGG AAGCGAAGGG AAAGAGTGTG ACAACCTGTT CACCGTCATT GCCCATTTAT 600
ACAACTTCCA CGTGGTACAG TCTCTCCTCA TCTTCGACAT TTTGAAAAAA CTGATTGGAA 660
CTTTCACCGA AAAAGATATT GAACTGATCT TGTTAATGCT GAAAAACGTG GGTTTTTCAT 720
TGAGGAAAGA TGATGCTTTA TCACTTAAGG AATTGATCAC TGAAGCCCAG ACCAAAGCCA 780
GCGGGGCAGG CAGCGAGTTT CAGGACCAGA CCAGGGTACG CGTGCGACGC TTGATCTGCT 840
TCCTAAGTCC CTAAAGCTCA CAACTGGCC AGAACCTAAA AATCAGTATC TGGGATTCGG 900
TTTATGCTAG AGACGATGTT GGCCCTGAAG AACAATGACA TCGCGAAAAT TCCAGGCTAT 960
GACCCCGAGC CCGTGGAGAA GCTGAGGAAA CTGCAGAGAG CTTTGGTCCG CAACGCCGGC 1020
TCAGGTTCTG AGACGAGCT TCGCGTCTCC TGGGACAGTG TCTTGAGTGC GGAGCAGACG 1080
GGTCGCTGGT GGATTGTGGG GTCCGCCTGG AGTGGGGCCC CGATGATCGA CAACAGTCAC 1140

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CATACGCACC TGCAGAAGCA GYTTGTGGGG ACGGTAGGGA CACCCATGYT CAAGGYTGCC 1200
 AGGCAGAGGC ACCCCCCTGT GTGGTGTGTG GTCCTGGCTT TACCTGGAGC AGCTCTCTTA 1260
 CTGTTCTTGA ATGGTCACTG AAATGTACAA GGTTTATCTG GAGGCCTTAC AGAAATTGCT 1320
 ATTAATATTA CATTGTGATA TAATTATTCC AAAAAAAAAA AAAAA 1365

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 180 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ala Ser Ile Ser Gly Gln Leu Glu Glu Leu Tyr Met Ala His Ser
 1 5 10 15
 Arg Lys Asp Met Asn Asp Thr Leu Thr Ser Ala Leu Met Gly Ala Cys
 20 25 30
 Val Thr Ala Ser Ala Met Pro Ser Arg Leu Met Met Glu His Val Leu
 35 40 45
 Leu Val Ser Ile Leu His His Thr Val Gly Ile Glu Val Gly Ala His
 50 55 60
 Phe Leu Glu Ala Val Val Arg Lys Phe Asp Ala Ile Tyr Lys Tyr Gly
 65 70 75 80
 Ser Glu Gly Lys Glu Cys Asp Asn Leu Phe Thr Val Ile Ala His Leu
 85 90 95
 Tyr Asn Phe His Val Val Gln Ser Leu Leu Ile Phe Asp Ile Leu Lys
 100 105 110
 Lys Leu Ile Gly Thr Phe Thr Glu Lys Asp Ile Glu Leu Ile Leu Leu
 115 120 125
 Met Leu Lys Asn Val Gly Phe Ser Leu Arg Lys Asp Asp Ala Leu Ser
 130 135 140
 Leu Lys Glu Leu Ile Thr Glu Ala Gln Thr Lys Ala Ser Gly Ala Gly
 145 150 155 160
 Ser Glu Phe Gln Asp Gln Thr Arg Val Arg Val Arg Arg Leu Ile Cys
 165 170 175

Phe Leu Ser Pro
180

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1310 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CAAGCACCAG GAAGTCAAGA TGCAAGCACC AGCCTTCAGG GACAAGAAAC AGGGGGTCTC	60
AGCCAAGAAT CAAGGTGCCC ATGACCCAGA CTATGAGAAT ATCACCTTGG CCTTCAAAAA	120
TCAGGACCAT GCAAAGGGTG GTCATTACAG ACCCACGAGC CAAGTCCCAG CCCAGTGCAG	180
GCCGCCCTCA GACTCCACCC AGGTCCCCCTG CTGGTTGTAC AGAGCCATCC TGAGCCTGTA	240
CATCCTCCTG GCCCTGGCCT TTGTCTCTG CATCATCCTG TCAGCCTTCA TCATGGTGAA	300
GAATGCTGAG ATGTCCAAGG AGCTGCTGGG CTTTAAAAGG GAGCTTTGGA ATGTCTCAAA	360
CTCCGTACAA GCATGCGAAG AGAGACAGAA GAGAGGCTGG GATTCCGTTC AGCAGAGCAT	420
CACCATGGTC AGGAGCAAGA TTGATAGATT AGAGACGACA TTAGCAGGCA TAAAAACAT	480
TGACACAAAG GTACAGAAAA TCTTGGAGGT GCTGCAGAAA ATGCCACAGT CCTCACCTCA	540
ATAAATGAGA GGACATTGTG GCAGCCAAAG CCACAACCTG GAAGATGGGG CTGCACCTGC	600
CAACGAAGAC GGGAAATGAC CCCCCCCCCC AGCCTAGTGT GAACCTGCCC CTCGTCCCAC	660
GTATAGAAAA ACCTCGAGTC ATGGTGAATG AGTGTCTCGG AGTTGCTCGT GTGTGTGTAC	720
ACCTGCGTGC GTGTGTGTGC GTGTGTGCGC GTGTGTTTCT GTATGTGCGT GTGTGCGTGC	780
GCGTGTGTGT GCATTTTGCA AAGGGTGGAC ATTTCACTGT ATCTCCCAGA AAGGTGAKGA	840
ATGAATAGGA CTGAGAGTCA CAGTGAATGT GGCATGCATG CCTGTGTCAT GWGACATATG	900
TGAGTCTCGG CATGTCACGG TGGGTGGCTG TGTGTGAGCA CCTCCAGCAG ATGTCACTCT	960
GAGTGTGGGT GTTGGTGACA TGCATTGCAC GGGCCTGTCT CCCTGTTTGT GTAAACATAC	1020
TAGAGTATAC TGCGGCGTGT TTTCTGTCTA CCCATGTCAT GGTGGGGGAG ATTTATCTCC	1080
GWACATGTGG GTGTGCGCAT GTGTGCCCTG TCACTATCTG TGGCTGGGTG AACGGCTGTG	1140

TCATTATGAG TGTGCCGAGT TATGCCACCC TGTGTGCTCA GGGCACATGC ACACAGACAT 1200
 TTATYTYTGC ACTCACATTT TGTGACTTAT GAAGATAAAT AAAGTCAAGG GAAAACAGCG 1260
 TCMAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1310

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 174 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Gln Ala Pro Ala Phe Arg Asp Lys Lys Gln Gly Val Ser Ala Lys
 1 5 10 15
 Asn Gln Gly Ala His Asp Pro Asp Tyr Glu Asn Ile Thr Leu Ala Phe
 20 25 30
 Lys Asn Gln Asp His Ala Lys Gly Gly His Ser Arg Pro Thr Ser Gln
 35 40 45
 Val Pro Ala Gln Cys Arg Pro Pro Ser Asp Ser Thr Gln Val Pro Cys
 50 55 60
 Trp Leu Tyr Arg Ala Ile Leu Ser Leu Tyr Ile Leu Leu Ala Leu Ala
 65 70 75 80
 Phe Val Leu Cys Ile Ile Leu Ser Ala Phe Ile Met Val Lys Asn Ala
 85 90 95
 Glu Met Ser Lys Glu Leu Leu Gly Phe Lys Arg Glu Leu Trp Asn Val
 100 105 110
 Ser Asn Ser Val Gln Ala Cys Glu Glu Arg Gln Lys Arg Gly Trp Asp
 115 120 125
 Ser Val Gln Gln Ser Ile Thr Met Val Arg Ser Lys Ile Asp Arg Leu
 130 135 140
 Glu Thr Thr Leu Ala Gly Ile Lys Asn Ile Asp Thr Lys Val Gln Lys
 145 150 155 160
 Ile Leu Glu Val Leu Gln Lys Met Pro Gln Ser Ser Pro Gln
 165 170

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GNGGCATCAGA CATTGGGGAG TGATTCAA

29

- (2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

CNTGAGAGAAC CTTTGCTTCC TGCTATAT

29

- (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CNATGCACTCC AGTGAGCTAG ATTCTTTA

29

- (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TNAATTGTGAG ATCTTCTCTC CAAGCTCT

29

- (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GNCGGTCTGGA AGCCATCCTC AACTGAAG

29

- (2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ANCTCTTCCTG GTGAAGGATG TTCATGTT

29

- (2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CNTTATGGAGG GTGAAGGAGT GATCTGGT

29

- (2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ANGTCCACTGT CTCCTCAGCT TGCCTCAC

29

- (2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GNTTGCATCTT GACTTCCTGG TGCTTGTA

29

- (2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 307 amino acids
 - (B) TYPE: amino acid

(C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met	Ser	Leu	Ala	Ser	His	Lys	Phe	His	Arg	Tyr	Ser	Cys	Ala	His	Cys	1	5	10	15
Arg	Lys	Pro	Phe	His	Lys	Ile	Glu	Thr	Leu	Tyr	Arg	His	Cys	Gln	Asp	20	25	30	
Glu	His	Asp	Asn	Glu	Ile	Lys	Ile	Lys	Tyr	Phe	Cys	Gly	Leu	Cys	Asp	35	40	45	
Leu	Ile	Phe	Asn	Val	Glu	Glu	Ala	Phe	Leu	Ser	His	Tyr	Glu	Glu	His	50	55	60	
His	Ser	Ile	Asp	Tyr	Val	Phe	Val	Ser	Glu	Lys	Thr	Glu	Thr	Ser	Ile	65	70	75	80
Lys	Thr	Glu	Asp	Asp	Phe	Pro	Val	Ile	Glu	Thr	Ser	Asn	Gln	Leu	Thr	85	90	95	
Cys	Gly	Cys	Arg	Glu	Ser	Tyr	Ile	Cys	Lys	Val	Asn	Arg	Lys	Glu	Asp	100	105	110	
Tyr	Ser	Arg	Cys	Leu	Gln	Ile	Met	Leu	Asp	Lys	Gly	Lys	Leu	Trp	Phe	115	120	125	
Arg	Cys	Ser	Leu	Cys	Ser	Ala	Thr	Ala	Gln	Asn	Leu	Thr	Asp	Met	Asn	130	135	140	
Thr	His	Ile	His	Gln	Val	His	Lys	Glu	Lys	Ser	Asp	Glu	Glu	Glu	Gln	145	150	155	160
Gln	Tyr	Val	Ile	Lys	Cys	Gly	Thr	Cys	Thr	Lys	Ala	Phe	His	Asp	Pro	165	170	175	
Glu	Ser	Ala	Gln	Gln	His	Phe	His	Arg	Lys	His	Cys	Phe	Leu	Gln	Lys	180	185	190	
Pro	Ser	Val	Ala	His	Phe	Gly	Ser	Glu	Lys	Ser	Asn	Leu	Tyr	Lys	Phe	195	200	205	
Thr	Ala	Ser	Ala	Ser	His	Thr	Glu	Arg	Lys	Leu	Lys	Gln	Ala	Ile	Asn	210	215	220	
Tyr	Ser	Lys	Ser	Leu	Asp	Met	Glu	Lys	Gly	Val	Glu	Asn	Asp	Leu	Ser	225	230	235	240

Tyr Gln Asn Ile Glu Glu Glu Ile Val Glu Leu Pro Asp Leu Asp Tyr
245 250 255

Leu Arg Thr Met Thr His Ile Val Phe Val Asp Phe Asp Asn Trp Ser
260 265 270

Asn Phe Phe Gly His Leu Pro Gly His Leu Asn Gln Gly Thr Phe Ile
275 280 285

Trp Gly Phe Gln Gly Thr Val Asn Lys Lys Asn Lys Arg Lys Leu Phe
290 295 300

Pro Thr Ser
305

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 61 to nucleotide 642;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 89 to nucleotide 440;
 - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;
 - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;
 - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;
 - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
 - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
 - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
 - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
 - (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).
2. A composition of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.
3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein encoded by a composition of claim 2, which process comprises:
 - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
 - (b) purifying said protein from the culture.
6. A protein produced according to the process of claim 5.
7. The protein of claim 6 comprising a mature protein.
8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
 - (a) the amino acid sequence of SEQ ID NO:2;
 - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127;
 - (c) fragments of the amino acid sequence of SEQ ID NO:2; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;the protein being substantially free from other mammalian proteins.
9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127.
11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.
12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.
14. A composition comprising an isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1625 to nucleotide 1750;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1484 to nucleotide 1729;
 - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;
 - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;
 - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;
 - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
 - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;
 - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
 - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
 - (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).
15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
 - (a) the amino acid sequence of SEQ ID NO:4;

- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35;
 - (c) fragments of the amino acid sequence of SEQ ID NO:4; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;
- the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 99 to nucleotide 1058;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 644;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 237 to nucleotide 1184;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 207 to nucleotide 935;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;
- (b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233;
- (c) fragments of the amino acid sequence of SEQ ID NO:8; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 142 to nucleotide 828;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 522;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127;

(c) fragments of the amino acid sequence of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 3 to nucleotide 1937;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 204 to nucleotide 414;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137;

- (c) fragments of the amino acid sequence of SEQ ID NO:12; and
- (d) the amino acid sequence encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290; the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 137 to nucleotide 457;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 323 to nucleotide 457;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 82 to nucleotide 322;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14;
 - (b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62;
 - (c) fragments of the amino acid sequence of SEQ ID NO:14; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;
- the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 312 to nucleotide 851;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 56 to nucleotide 470;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
 - (b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53;
 - (c) fragments of the amino acid sequence of SEQ ID NO:16; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;
- the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 541;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 272 to nucleotide 541;

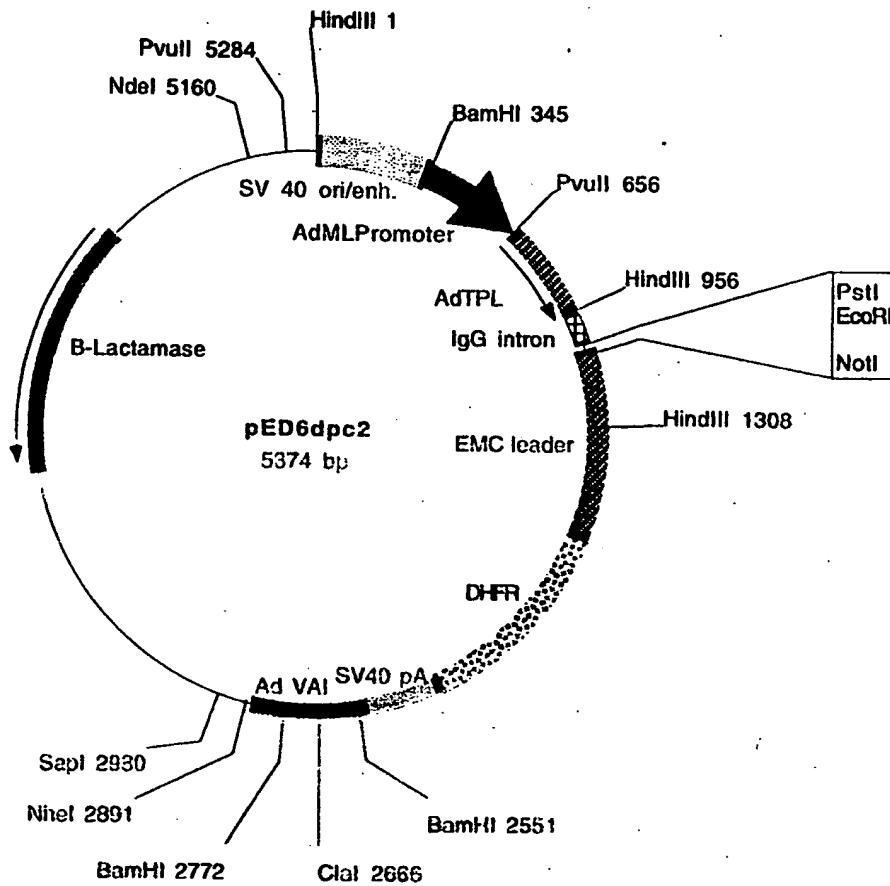
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 448;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:18;
 - (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143;
 - (c) fragments of the amino acid sequence of SEQ ID NO:18; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;
- the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.

FIGURE 1A

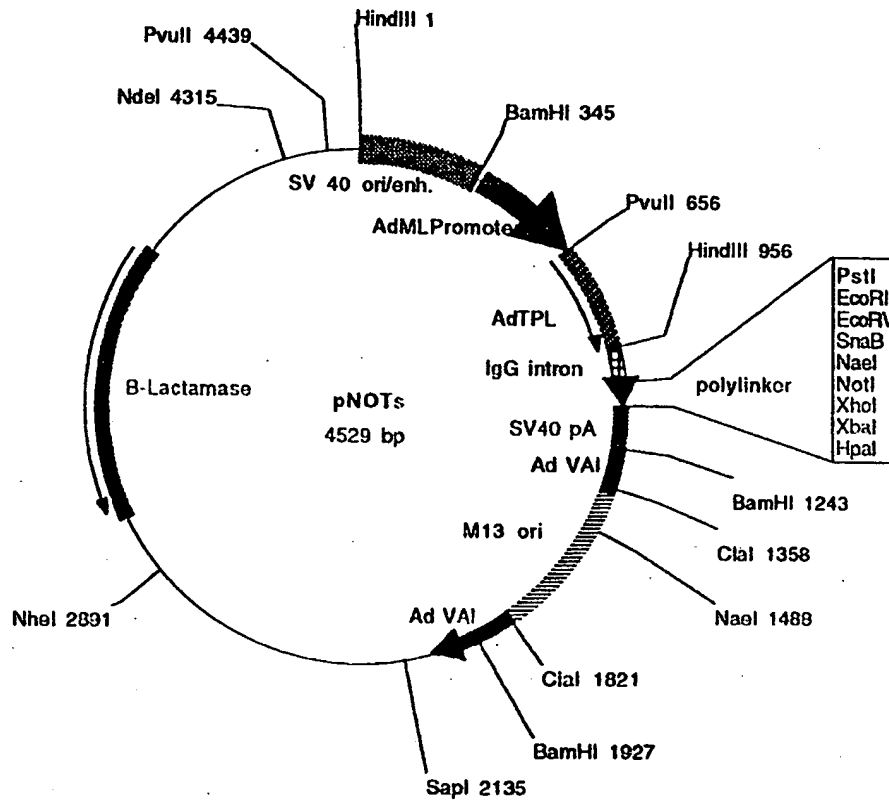


Plasmid name: pED6dpc2

Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs

Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al, 1989. Mol. Cell. Biol. 9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the Clal site. SST cDNAs are cloned between EcoRI and NotI